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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/914,152	NARIMATSU ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-25,29-31,33,38 and 48-54* is/are pending in the application.

4a) Of the above claim(s) *14-25,29-31,33,38,53 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-13 and 48-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 2-25, 29-31, 33, 38, 48-54 are currently pending in this application. Claims 2-13, 48-52 are now under consideration. Claims 14-25, 29-31, 33, 38, 53-54 remain withdrawn from consideration as drawn to non-elected invention.

Applicant's amendments and arguments filed on 11-19-03, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn the rejection under 35 U.S.C. 112, Ist paragraph for non-enablement due to a requirement of biological deposit, as applicant has now provided a certification under the "remarks" section, rejection of polynucleotide claims for lack of enablement and written description in view of claim amendments.

Rejoinder of restricted inventions

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312. In the event of rejoinder, the requirement for restriction between the

product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. **Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112.** Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. **Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined.** See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to rejoin, in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

As claims drawn to the product (i.e., the polypeptide and the polynucleotide) remain non-allowable, Examiner continues to maintain the restriction as indicated in the previous Office action.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). However, the priority document is in Japanese language and applicants have not filed an English language translation for the same. Applicant is urged to file the translation in order to perfect the foreign priority.

Claim Objections

Claim 51 is objected to because of the following informalities: Claim 51 recites the phrase "under stringent conducting". The word "condition" appears to be incorrectly spelled as "conducting". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50, 3-4, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide with SEQ ID NO:1 or the amino acid sequence comprising amino acids 31-310 of SEQ ID NO:1 and having ß 1,3-galactosyltransferase activity, does not reasonably provide enablement for such a polypeptide having the same activity but wherein one to twenty amino acids have been deleted, replaced or added. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 50, 3-4 are so broad as to encompass variant ß 1,3-galactosyltransferase wherein those skilled in the art have not been taught as to how to make said polypeptides. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to undue experimentation required for making said polypeptides and the large number of ß 1,3-galactosyltransferases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity, requires a knowledge of and guidance with regard to which specific amino acids in the protein's sequence, if any, are tolerant to modification and which are conserved (i.e. expectedly intolerant to modification), and a detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the single nucleotide and encoded amino acid sequence of only one ß 1,3-galactosyltransferase. It would require undue experimentation by the skilled artisan to make and use the claimed polypeptides. The specification is limited to teaching the making of the polypeptide with SEQ ID NO: 1 as ß 1,3-galactosyltransferase but provides no guidance with regard to the making of variants/mutants or provides no guidance with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide's primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention

would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to make/use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments including variants, mutants or recombinants having the same activity but wherein one to twenty amino acids have been deleted, replaced or added to SEQ ID NO:1, because the specification does not establish: (A) regions of the protein structure (SEQ ID NO:1)which may be modified by deleting, replacing or adding one to twenty amino acids to SEQ ID NO:1. without effecting the ß 1,3-galactosyltransferase activity; (B) the general tolerance of ß 1,3-galactosyltransferase activity, to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any or all ß 1,3-galactosyltransferase amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope

of the claims broadly including variants of ß 1,3-galactosyltransferases with an enormous number of amino acid modifications of SEQ ID NO: 1. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of ß 1,3-galactosyltransferase polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants have traversed the above rejection arguing that they have cancelled claims 1 and limited the number of changes to be made to the polypeptide between 1-20 amino acids. However, such an argument and the amendment are not persuasive to overcome the above rejection because of the reasons explained in the above rejection. Reiterating from the above rejection, while methods to produce variants of a known polypeptide sequence by using techniques such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e., changing from (any)one to twenty amino acids) requires that one of ordinary skill in the art know or be provided with guidance for the selection of specific amino acids in the polypeptides that can be modified and which of the large number of variants that result from such modification have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the

experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure (SEQ ID NO:1)which may be modified by deleting, replacing or adding one to twenty amino acids to SEQ ID NO:1. without effecting the ß 1,3-galactosyltransferase activity; (B) the general tolerance of ß 1,3-galactosyltransferase activity, to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any or all ß 1,3-galactosyltransferase amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Therefore the above rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2-9, 11-13, 48-52 are rejected under 35 U.S.C. 102(a) as being anticipated by Isshiki et al. (J. Biol. Sci. Vol., 274(18):12499-12507, Apr. 1999) or Zhou D et al. (Eur. J. Biochem.Vol. 263(2) :571-576). This rejection is based upon the public availability of a printed publication in this country prior to the date of filing. Claims 2-13, 48-52 of the instant application are drawn to polypeptides having ß 1,3-galactosyltransferase activity involved in synthesis of sialyl-Lewis sugar chain, wherein the polypeptide consists of an amino acid sequence with SEQ ID NO:1 or such a polypeptide wherein the from one to twenty amino acids have been deleted, replaced or

added, wherein the polypeptide activity is transferring galactose via ß 1,3-linkage to N-acetylglucosamine present at the non-reducing end of the sugar chain, wherein the polypeptides are encoded by polynucleotide with SEQ ID NO:2 or polynucleotides capable of hybridizing under stringent conditions with SEQ ID NO:2, a recombinant DNA comprising said DNA, a host cell transformed with said DNA, wherein the host cell is a microbe, an animal cell or a plant cell, or wherein the host cell is an insect cell such as *Spodoptera frugiperda* cell, a process of making the polypeptide by culturing the host cell in an appropriate medium and collecting the accumulated polypeptide. Isshiki et al. and Zhou et al. disclose a polypeptide having an amino acid sequence that is 100% identical to SEQ ID NO:2 (see enclosed sequence alignment) and its respective encoding polynucleotide, which are capable of hybridizing to the polynucleotide with SEQ ID NO:1 under stringent conditions. The reference also discloses host cells such as insect cells, *Sp.frugiperda* transformed with polynucleotides encoding the above enzyme and method of making the polypeptide by culturing said transformed cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Isshiki et al. or Zhou D et al. as applied to claims 2-9, 12-13, 48-52 above, and further in view of the common knowledge in the art that *E.coli* is a robust host cell that can be used for expression of

heterologous polypeptides. Claims 10 is drawn to a transformant according to claim 9, wherein the microorganism is *E.coli*.

The reference of Isshiki et al. and Zhou et al. has already been discussed above. Zhou et al. disclose a transformed insect cell and Isshiki et al. disclose a transformed Namalwa cell. The references do not appear to teach or suggest the use of *E.coli*. However, with the above two references in hand, it would have been obvious to one of ordinary skill in the art --wherein it is common knowledge that *E.coli* can be used as a very good host cell for quick small-to-medium-scale production of heterologous polypeptides,-- to use the DNA sequence taught by Zhou et al. or Isshiki et al. and subclone it in appropriate vectors such that they can be used to transform *E.coli* and use it for production of the polypeptide. One of ordinary skill in the art would have been motivated to do so in order to make the polypeptide in larger quantities for further characterization. One of ordinary skill in the art would have a reasonable expectation of success since Zhou et al. or Isshiki et al. provide the polynucleotide encoding the polypeptide and art is rich in methods of transforming *E.coli*.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Manjunath N. Rao Ph.D.
Patent Examiner, A.U. 1652
1/30/04